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Pain management of newly diagnosed sarcoma patients at a single center

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Abstract

Background: Systematic pain management of children is insufficient in China, and there is no literature on pain in children with sarcoma.

Methods: Clinical data of 188 patients with newly diagnosed sarcoma admitted to the Medical Oncology Department of Beijing Children's Hospital was collected from October 2018 to December 2020. Children experiencing pain received analgesic treatment and regular assessment.

Results: Thirty-seven patients (19.7%) suffered from pain. Six cases (16.2%) had mild pain, 17 (46.0%) moderate, and 14 (37.8%) severe. Daily lives of 31 patients were affected by pain. Twenty-six cases had bone invasion. The analgesic rate was 54.1% before admission and 89.2% after admission. Nine cases were treated with oral morphine regularly, and their pain was relieved before chemotherapy; the dose of morphine was 0.14 ± 0.034 mg/kgQ4H when the target was reached. No serious adverse reactions were observed. The period of morphine application after chemotherapy was 5 to 9 days, and there was no withdrawal reaction.

Conclusion: Pain in children with newly diagnosed sarcoma was mainly moderate to severe, and the incidence of pain in sarcoma with bone invasion was higher, with greater intensity. Patients who received standardized pain assessment and regular analgesics reached pain relief quickly, and no serious adverse reactions were observed within the recommended dosage.

Abbreviations: ES = Ewing sarcoma, FLACC = face, legs, activity, cry, consolability, NRSTs = non-rhabdomyosarcoma soft tissue sarcomas, NSAIDS = non-steroidal anti-inflammatory drugs, RMS = rhabdomyosarcoma, WHO = World Health Organization.

Keywords: children; morphine, pain, sarcoma

1. Introduction

Sarcoma is a type of malignant tumor in children, and includes rhabdomyosarcoma (RMS), Ewing sarcoma (ES), osteosarcoma, non-rhabdomyosarcoma soft tissue sarcomas (NRSTs), etc. RMS and NRSTs originate from soft tissue,[1,2] osteosarcoma originates in bone,[3] and ES may occur in either bone or soft tissue.[4] Sarcoma has a high degree of malignancy, grows rapidly, and metastasizes easily; therefore, it can cause pain in the primary or metastasized sites because of compression, infiltration, bone damage, and nerve injury. Moreover, the operation and complications in the treatment process can also cause pain,[5] making pain 1 of the common symptoms of sarcoma. Although the importance of pain management in children has been gradually accepted in recent years, studies have shown that the systematic pain management of children is insufficient,[6] and there is no summary of the pain status of children with sarcoma. Since 2018, our center has carried out standardized pain

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The Ethics Committee of Beijing Children's Hospital of Capital Medical University (No. 2021-E-074-R) approved the study. And we got informed consent from all 188 participants.

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management for children newly diagnosed with solid tumors. This paper is a periodic summary of the situation of pain in newly diagnosed sarcoma patients, with an emphasis on the analgesic mode, providing a basis for the clinical management and drug treatment system.

2. Materials and Methods

2.1. Inclusion and exclusion criteria

Children newly diagnosed with sarcoma and admitted to the Medical Oncology Department of Beijing Children's Hospital from October 2018 to December 2020 were included. The exclusion criterion was non-sarcoma confirmed by pathological consultation after admission.

2.2. Pain management

In accordance with the public health strategy of the World Health Organization (WHO) and the current medical resources in China, the center adopts a part-time palliative therapy team mode to conduct pain management for pediatric cancer patients. The team consists of 2 oncology physicians who have been trained as part-time palliative care doctors, 1 pharmacist, and 1 experienced palliative care doctor. Combined with the education and guidance of parents, the team implements systematic pediatric pain management, collaborating with oncology physicians and nurses.

Process of management. Basic information about the patients was collected at admission, and pain assessment was completed. Thereafter, an analgesic plan was formulated by the part-time palliative care team and oncologists. The plan was started after getting informed consent from the patients' parents. For patients who had accepted effective and rational analgesics before admission, the original plan was continued. For other patients, a new analgesic plan was formulated based on the "WHO Guidelines for Drug Treatment of Persistent Pain Related to Childhood Diseases,"[7] "Shanghai Expert Consensus on Cancer Pain Diagnosis and Treatment 2017 Edition,"[8] and "Beijing Cancer Pain Management Standards 2017 Edition."[9] Pain, adverse reactions, and chemotherapy progress were recorded daily for children who received strong opioid analgesics.

Pain assessment. Pain assessment on admission included history, site, degree, and duration of pain; the impact on sleep, mood, daily activities, social interaction; and analgesics administered before admission. The pain degree was evaluated according to the WHO guidelines. Children aged under 4 or without expression ability were evaluated by the face, legs, activity, cry, consolability (FLACC) scale (including 5 aspects–face, legs, activity, crying, and consolability).[10] Children aged over 4 were evaluated using the Won-Baker Facial Expression Scale.[11] Scores of 1 to 3 are classified as mild pain, 4 to 6 as moderate, and 7 to 10 as severe. Other items were collected through questionnaires. In addition to the assessment on the day of admission, patients who accepted regular analgesics were evaluated before and 1 hour after each medication.

Analgesic drug application. The principles of drug therapy include applying step-by-step, on time, in an appropriate manner, and individually. Non-steroidal anti-inflammatory drugs (NSAIDS) were used for mild pain, and strong opioids were used for moderate-to-severe pain. For persistent pain, medication should be taken regularly. Due to the low weight of children and availability of opioids in our hospital, strong opioids were started with oral morphine as quick release tablets, 0.1 to 0.2 mg/kg each time (the final amount is determined according to the divisibility of the tablet), every 4 hours. The goal of analgesic use was defined as a pain degree of less than 4 and a pain frequency of less than 3 times per day. The dose was adjusted every 24 hours, referring to the titration process of adult controlled and sustained-release opioids. If the pain degree was 7 to 10, the dose was increased 50% to 100%, and if the pain degree was 4 to 6, the dose was increased 25% to 50%. If the goal was reached within 48 hours and no suspicious adverse reactions occurred, the dose was reduced after beginning chemotherapy. The principle was to maintain each dose and gradually reduce the frequency. Individualized programs were formulated.

Monitoring of adverse reactions. For patients who accepted morphine, adverse reaction were recorded daily, including constipation, urinary retention, nausea, vomiting, itchy skin, respiratory depression, and consciousness disturbance.

2.3. Statistical analysis

SPSS 22.0 (IBM, NY) was used for statistical analysis. Quantitative data was described in the form of a mean (standard deviation) if it followed a normal distribution, and as the median (upper and lower quartile) if it did not follow a normal distribution. The classified data was described by frequency (percentage).

3. Results

3.1. General clinical features

A total of 188 patients with newly diagnosed sarcoma were enrolled. The median age was 60 m (3–210 m). Among them, the proportion of those aged 4 to 9 year was the highest (78 cases, 41.5%), and the proportion of 10 year old and above was the lowest (37 cases, 19.7%). Primary diagnosis was rhabdomyosarcoma in 106 cases (56.4%), Ewing's sarcoma in 39 cases (20.7%), osteosarcoma in 6 cases (3.2%), and the other 37 cases (19.6%) (Table 1), which included 7 malignant rhabdomyoid tumors, 6 fibroblast/myofibroblast tumors, 3 malignant peripheral nerve sheath tumors, and undifferentiated hepatic sarcomas, 2 synovial sarcomas, 1 hemangiosarcoma, and 15 soft tissue sarcomas with indeterminate classification.

Table 1

General clinical features and incidence of pain in newly diagnosed sarcoma.

		n	Proportion (%)	Number of cases with pain	Incidence of pain(%)
Gender	Male	105	55.9	22	21.0
	Female	83	44.1	15	18.1
Age	<4	73	38.8	11	15.1
	4–9	78	41.2	20	25.6
	≥10	37	19.7	6	16.2
Diagnosis	RMS	106	56.4	16	15.1
	Others	37	19.7	2	5.4
	ES	39	20.7	14	35.9
	Osteosarcoma	6	3.2	5	83.3

ES = Ewing sarcoma, RMS = rhabdomyosarcoma.

3.2. Clinical features of patients with pain

Of the 188 patients, 37 (19.7%) diagnosed with sarcoma suffered from pain. The incidence of pain in different genders, age groups, and tumors is shown in Table 1. The incidence of pain in children aged 4 to 9 years was the highest (20/78, 25.8%), followed by children aged 10 years and above (16.2%), and children under 4 years old (15.1%). The incidence of pain in children with osteosarcoma was significantly higher than that of other diseases (5/6, 83.3%), followed by Ewing's sarcoma (14/39, 35.9%), rhabdomyosarcoma (16/105, 15.1%) and other sarcomas (2/37, 5.4%).

Among 37 sarcoma patients with pain at diagnosis, 26 (70.3%) had bone invasion, a higher proportion than those without bone invasion (29.7%). None of the 37 children had their primary tumors resected when they visited our center (Table 2).

4. Characteristics of pain

4.1. Basic characteristic

The course of pain before admission was 2 days to 5 months (median 1 month). Their pain all occurred at the site of primary tumor, and 8(21.6%) cases had pain at metastatic sites meanwhile. The pain degree was mild in 6 cases (16.2%), moderate in 17 cases (46.0%), and severe in 14 cases (37.8%). The pain duration per day was less than 1 hour in 21 cases (56.8%), 1 to 10 hours in 10 cases (27.0%), and more than 10 hours in 6 cases (16.2%). In the 5 cases of osteosarcoma patients who suffered from pain, the pain degree was moderate to severe (100%), the proportion of which was higher than that of RMS (14/16, 87.5%) and ES (11/14, 78.6%). Of the 26 cases with bone invasion who suffered from pain, 21 (80.8%) had moderate-to-severe pain. In the 6 cases of adolescents (10 years old or above) who suffered from pain, 4 (66.7%) had severe pain, which was higher than that of patients aged 4–9 years old (8/20, 40%) and under 4 years old (2/11, 18.2%).

4.2. Influence on daily life

Thirty-one (83.8%) of the 37 patients with pain were affected by pain in their daily lives. The main manifestation was the influence on emotions, followed by sleep and daily activities. Pain affected sleep in 23 cases (62.2%), which was manifested as an inability to fall asleep or awaken because of pain. 27 cases (73.0%) were affected by emotion, among which restlessness was the most common, followed by larmoyant and depression. In 18 cases (48.6%), daily activities were affected, such as difficulty in sitting, standing, and walking (Table 3). Compared to the proportion of moderate and severe pain, 4 (66.7%) of the 6 cases of adolescents with pain were affected by emotions, which was lower than that of children under 4 years old (9/11, 81.2%) and those aged 4 to 9 (14/20, 70%).

Table 2

General clinical features of patients who suffered from pain.

		n	Proportion (%)
Gender	Male	22	59.5
	Female	15	40.5
Age	<4	11	20.7
	4–9	20	54.1
	≥10	6	16.2
Diagnosis	Rhabdomyosarcoma	16	43.2
	Ewing sarcoma	14	37.8
	Osteosarcoma	5	13.5
	Malignant rhabdomyoid tumor	1	2.7
	Soft tissue sarcoma	1	2.7
Bone invasion	Yes	26	70.3
	No	11	29.7
Tumor resected	Yes	0	0
	No	37	100

Table 3

Influence on daily life of pain in newly diagnosed sarcoma.

	Influence	n	Proportion (%)	Manifestation	n	Proportion (%)
Sleep	Yes	23	62.2	Wake up by pain <once/d	5	21.8
				1-5 times/d	7	30.4
				>5 times/d	4	17.4
				Difficult to fall asleep	7	30.4
	No	14	37.8	–	–	–
Emotion	Yes	27	73	Restless	14	51.9
				Larmoyant	9	33.3
				Depressed	4	14.8
	No	10	27	–	–	–
Daily activities	Yes	18	48.6	Difficult to sit	4	22.2
				Difficult to stand	4	22.2
				Difficult to walk	10	55.6
	No	19	51.4	–	–	–

4.3. Analgesics before admission

In the 37 cases with pain at diagnosis, 20 (54.1%) received analgesics before admission. The analgesic rate of patients with moderate and mild pain was 16.7% (1/6) before admission, all using oral ibuprofen, and it was effective. The analgesic rate of children with moderate and severe pain was 61.3% (19/31), among which 68.4% (13/19) were treated with NSAIDS, 26.3% (5/19) with weak opioids (tramadol and codeine), and 5.3% (1/19) with strong opioids (oxycodone). The effectiveness of analgesics before admission and the reasons for those who did not receive analgesics are shown in Table 4. In patients with moderate and severe pain who did not receive analgesics, half of the parents believed that their children did not need analgesics.

4.4. Analgesics after admission

The analgesics after admission of 37 cases with pain are shown in Figure 1. 33 patients (89.2%) received analgesics. The analgesic rate for mild pain was 83.3% (5/6), and ibuprofen was effective in all patients. The rate of moderate and severe pain was 90.3% (28/31). Among the 28 patients, 6 had previously received effective analgesics, including 4 with ibuprofen. Two cases were given tramadol, but both had significant pain that was inadequately controlled after admission, necessitating the switch to morphine. Analgesic plans were reformulated for the remaining 22 children after admission, and oral morphine was recommended for 21 of them. Among these 21 cases, 1 did not obtain opioids on the day of admission, and the pain score was under 3 after chemotherapy on the second day of admission, so morphine was not administered. Another 12 cases did not receive morphine due to the refusal or rejection of parents (57.1% of all children recommended to receive morphine). All 12 children received ibuprofen when necessary, and their pain was relieved after chemotherapy. The time from admission to pain relief was 4–10 days (median = 7 days).

Ten cases were finally treated with morphine. The dose, effect, duration, and adverse reactions of morphine are shown in Table 5. The actual initial dose of morphine was 0.12 ± 0.035 mg/kg Q4H. Case 1 refused to continue using morphine due to a severe digestive tract reaction and was discharged without chemotherapy, and whether the pain was relieved remains unknown. The other 9 cases got pain relief before chemotherapy, and their sleep and emotions recovered normally. Among them, the initial dose of 2 cases did not reach the analgesic goal, so the dose was increased. The final dose of morphine was 0.14 ± 0.034 mg/kg Q4H. The time of morphine dose reduction after chemotherapy was 1 to 4 days (median = 7 days), and the total time of morphine application was 1 to 20 days (median = 7 days).

In terms of adverse reactions, case 1 developed nausea and vomiting and was discharged. Case 2 showed a decrease in percutaneous oxygen saturation 1 day after morphine administration, which was relieved after morphine withdrawal and other treatment. Four cases who had constipation at admission accepted morphine together with lactulose and glycerin enema, and no aggravation of constipation occurred. There were no other adverse reactions such as uroschesis or change of consciousness. No withdrawal reactions occurred during drug withdrawal.

5. Discussion

The International Association for the Study of Pain defines pain as an unpleasant feeling or emotional experience associated with existing or potential tissue damage.[12] Therefore, pain is composed of physiological, cognitive, emotional, and other components. It is subjective and may occur in adults or children. Cancer is the leading cause of death by disease in children.[13] For children with cancer, pain is a common and torturous symptom.[14] Although there are few accurate data reports on the current status of pain in children, studies have shown that almost all children with cancer experience pain.[5] Perri et al investigated pain in 230 children with cancer. Three quarters of the parents reported that their children had pain, among which mild, moderate, and severe pain accounted for 3.9%, 41%, and 59%, respectively.[14] Uncontrolled pain can cause a series of adverse consequences, such as decreased quality of life, sleeping disturbances, increased sensitivity to pain, emotional and behavioral problems, etc.[14] Meanwhile, the pain of children also aggravates their parents' anxiety and stress disorders,[15] and even causes troubles for their siblings. Cancer-related pain includes that caused by the disease itself and the operations in the treatment process.[14] Our preliminary investigation indicated that pain related to primary disease was the main cause of pain in solid tumors.[16] This study showed that the incidence of pain in children with newly diagnosed sarcoma was 19.7%. When first admitted, the primary tumor was not removed, and pain mainly occurred in the primary site. Moderate and severe pain were the majority (83.7%). Some had pain for a long time, and 6 cases (16.2%) suffered from pain for more than 10 hours per day. Pain affects sleep, mood, and daily physical activities of most children, which seriously affects their quality of life and their coordination for examination and treatment. Therefore, the pain of a newly diagnosed sarcoma should be paid attention to and actively treated.

Table 4

Analgesic before admission of newly diagnosed sarcoma.

Pain degree	Analgesic	n	Proportion					
Mild	Yes	1	16.7%	Drug			n of remission	Ratio of remission
				NSAIDS			1	100%
	No	5	83.3%	Reason			n	Proportion
				Insufficient attention			4	80%
				Fear of adverse reactions			1	20%
Moderate/severe	Yes	19	61.3%	Drug	n	Proportion	n of remission	Ratio of remission
				NSAIDS	13	68.4%	4	30.8%
				Weak opioids	5	26.3%	2	40.0%
				Strong opioids	1	5.3%	0	0
	No	12	38.7%	Reason			n	Proportion
				Insufficient attention			6	50.0%
				Fear of adverse reactions			4	33.3%
				No access to drugs			1	8.3%
				Difficult to take medicine			1	8.3%

NSAIDS = non-steroidal anti-inflammatory drugs.

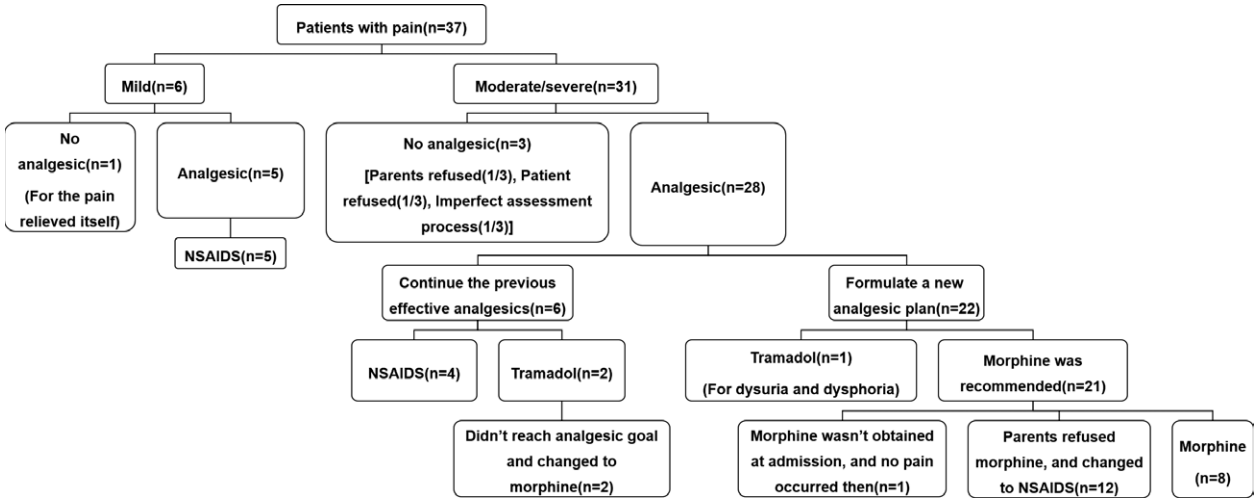

Figure 1 . Analgesics after admission of newly diagnosed sarcoma.

Table 5

Dose, effect, course and adverse reaction of morphine.

	Initial dose (mg/kgQ4H)	Regular medication	Dose to reach analgesic goal (mg/kgQ4H)	Time to reach analgesic goal	Duration of morphine (d)	Pain relieved before chemotherapy	Days after beginning of chemotherapy when dose reduced (d)	Adverse reaction
1	0.104	No	–	–	1	–	–	Nausea and vomitting
2	0.132	No	0.132	≤24 h	1*	Yes	–	Oxygen saturation reduction
3	0.180	Yes	0.180	≤24 h	7	Yes	2	No
4	0.117	Yes	0.117	24–48 h	6†	No	–	No
5	0.164	Yes	0.164	≤24 h	13	Yes	2	No
6	0.126	Yes	0.126	24–48 h	7	No	1	No
7	0.148	Yes	0.148	≤24 h	7	Yes	4	No
8	0.066	Yes	0.066	≤24 h	10	Yes	4	No
9	0.125	Yes	0.17‡	24–48 h	12	Yes	4	No
10	0.080	Yes	0.133‡	24–48 h	20	Yes	1	No

* Oxygen saturation decreased after 1 d of morphine application, so it was discontinued.

† The patient transferred to intensive care unit and changed to other analgesics after 6 d of morphine application.

‡ The pain degree was 4–6 within 24 h, and the dose was increased.

Among the sarcomas involved in this study, RMS and NRSTs originated from soft tissue, osteosarcoma originated from bone, and ES may have originated from both. This study showed the incidence and severity of pain in ES and osteosarcoma were higher than those of other types, and on the other hand, among the 37 children with pain, 26 (70.3%) had tumors of bone origin or invasion, and moderate-to-severe pain accounted for 80.8%. It is speculated that tumors with bone invasion may cause a higher incidence and severity of pain. The literature suggests tumor cells release pain-promoting substances, including bradykinin, prostaglandin, etc., and the number, size, and activity of osteoclasts can be significantly increased, eventually leading to fractures. Bone tumor growth can also cause neuropathic pain by directly damaging nerve fibers and inducing pathological changes in sensory and sympathetic nerves,[17,18] and neuropathic pain is considered to be more likely to cause chronic pain and is less sensitive to analgesics.[19] In addition, this kind of pain may be different from others in characteristics due to its special source, such as electric pain and burning pain. As the subjects of our study are children, who have difficulty describing the characteristics of pain, we did not collect any associated data. In the future, studies for the assessment of older children can increase pain characteristics.

The results of this study show that the proportion of severe pain in adolescents was higher than that of other age groups. However, according to the questionaires of parents, the proportion of adolescents' pain affecting their emotion was lower than others. Teenagers experience rapid physical development and change of social identity, so there may be some specific problems in the treatment process, such as the main role of monitoring and reporting pain transfers from parents to patients themselves.[20] Adolescents' special physiological and psychological characteristics lead to higher sensitivity to pain, while their improved sense of independence may lead to unmatched external emotional changes. Thus, pain assessment should be based on the patient's rather than others' speculation. At present, there are no specific reports on the detailed characteristics of pain experience in adolescents with cancer,[20] and it is necessary to collect sufficient data to understand the characteristics of pain in adolescents.

For infants and young children, the discovery of pain is more difficult due to the limited ability of self-expression. Previous studies have explored a series of assessment tools mainly based on behavior, such as neonatal-infant pain scale, FLACC, children's hospital of eastern ontario pain scale, etc. However, the perspective of their parents or long-term caregivers should be taken into consideration, as they can describe the children's pain

best.[5] In this study, the incidence of pain in the age group of under 4 years was the lowest (15.1%). No specific data on the incidence of infant sarcoma in the extent literature was found. The pain of this age group in our study was reported by the long-term caregivers of the children, and the FLACC scale recommended by WHO was used to determine the pain degree under the guidance of clinicians; thus, the pain status was theoretically more comprehensive. It should be noted that details of daily life play an important role in pain assessment, which requires trust between families and doctors.

In this study, the median duration of pain before admission was 1 month, and the longest was 5 months. Only 54.1% of them received analgesics before admission. For moderate and severe pain, most accepted NSAIDS, some accepted weak opioids, which are not recommended for children now, and the few who use strong opioids chose oxycodone, which is also not recommended for children; moreover, the dose was significantly higher than the correct dose. The situation may be related to insufficient attention to pain and cognition of analgesics and the difficulty of obtaining opioids.[7] The effective rate of NSAIDS for moderate and severe pain before admission was only 30.8%, and that of weak opioids was only 40.0%. Literature has revealed that the efficacy and safety of weak opioids in children is still controversial.[7] The only child who received a strong opioid before admission did not get pain relief. After admission, 61.9% of the parents still refuse the administration of morphine, mainly because of the opinion that children do not need analgesics and fear of the adverse reactions. The pain relief time for them was longer than that of those who used morphine. Previously, Tutelman reported that parents have misconceptions about pain assessment and management, and the most commonly used analgesic drugs by parents are also NSAIDS.[14] However, parents in this study did not express concerns about opioid addiction.

In contrast to the condition above, 55.6% of the patients who regularly received morphine after admission achieved the analgesic goal within 24 hours, and the rest of them within 24 to 48 hours. Sleep and emotional state also improved significantly. The actual morphine dose was 0.14 ± 0.034 mg/kgQ4H, which was lower than the recommendation of WHO (0.2–0.4 mg/kgQ4H for 1–2 year old children, 0.2–0.5 mg/kgQ4H for 2–12 year old). Most patients reduce and discontinue analgesic on a regular basis. One child showed a decrease in oxygen saturation 1 day after morphine administration, and although the possibility of respiratory depression from morphine was considered, the primary disease was RMS with central nervous system invasion, and the patient had bilateral unequal pupils at the same time, indicating possible progression of the primary disease. Therefore, whether it was related to morphine could not be determined. No other serious adverse reactions occurred, such as respiratory depression, addiction, and urinary retention, which are usually concerning to parents and clinicians. Some children were already constipated when they were admitted, and it was not aggravated after morphine application. Previous studies have also shown that the use of low-dose opioids and titrated analgesics is the best strategy for pain management.[12] The results above suggest that patients with moderate and severe pain should regularly use morphine rather than wait for pain relief after chemotherapy or try NSAIDS and weak opioids. As some children with moderate pain had been using NSAIDS and getting pain relief before admission, they could be continued after admission. Additionally, 1 of the children who accepted morphine reached analgesic goal within 48 hours, but experienced twice the dose as the primary diagnosis was unclear and chemotherapy could not start, suggesting more attention to similar conditions.

The pain in children with newly diagnosed sarcoma was mainly moderate to severe, and the incidence of pain in sarcoma originating from bone or invading bone was higher, with greater intensity. Patients who received standardized pain assessment and regular analgesics reached pain relief quickly, and no serious adverse reactions were observed within the recommended dosage.

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Author contributions

XLM, XN, and XZ designed the idea for this article and managed the cases. PYY, YS, WZ, and CD collected clinical data. PYY, YCZ, YL, LW, and XZ are responsible for assessing pain and developing an analgesic plan. PYY and SYC analyzed and interpreted the patients' data. PYY, XZ, XN, and XLM were major contributors in writing the manuscript. All authors were involved in drafting, reviewing, and approving the final version for submission.

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